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ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/576,690	MCSWIGGEN ET AL.	
	Examiner	Art Unit	
	Terra C. Gibbs	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *October 3, 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,13-21,30,31 and 36-47* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3, 13-21, 30, 31, and 36-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 April 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is a response to Applicant's Election filed October 3, 2007.

Claims 2, 4-12, 22-29, and 32-35 have been canceled. New claims 36-47 are acknowledged. Claims 1, 3, 13-21, 30, and 31 have been amended.

Claims 1, 3, 13-21, 30, 31, and 36-47 are pending in the instant application.

Claims 1, 3, 13-21, 30, 31, and 36-47 have been examined on the merits.

Election/Restrictions

The previous Restriction Requirement mailed July 20, 2007 is moot in view of Applicant's Amendment filed October 3, 2007 to cancel claim 33.

Information Disclosure Statement

It is noted that Applicants have not filed an information disclosure statement under § 1.97(c). Applicant is reminded of 37 CFR § 1.56, which details Applicants duty to disclose all information known to be material to patentability.

Drawings

The drawings filed on April 21, 2006 are acknowledged and have been accepted by the Examiner.

Priority

It is noted that the instant application claims priority to a laundry list of U.S.

Provisional Applications and pending U.S. Patent Applications. The reference should be updated to reflect applications for patents that are pending or that have been abandoned. Second, due to the voluminous nature and number of the applications to which priority is claimed, Applicant are requested to point out with particularity where support for the instantly claimed invention may be found in one or more of the prior filed applications to which benefit is claimed, since such support is not readily apparent in the priority documents.

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

It is further noted that claims 1, 3, 13-21, 30, 31, 36-41, and 46 are drawn to a chemically modified nucleic acid molecule comprising a sense strand and an antisense strand wherein the antisense strand is complementary to a human NOGO receptor RNA comprising SEQ ID NO:325, wherein each strand is 18 to 27 nucleotides in length, wherein about 50 to 100% of the nucleotides in each of the sense and antisense strands of the chemically modified double stranded nucleic acid molecule are modified with modifications selected from 2'-O-methyl, 2'-deoxy-2-'fluoro, 2'-deoxy, phosphorothioate and deoxyabasic modifications and a method of use therein. Claims 44, 45, and 47 are drawn to a chemically modified nucleic acid molecule comprising a

sense strand and an antisense strand wherein the antisense strand is complementary to a human NOGO receptor RNA comprising SEQ ID NO:325, wherein each strand is 18 to 27 nucleotides in length, wherein at least 50% of the nucleotides in each of the sense and antisense strands of the chemically modified double stranded nucleic acid molecule are modified with modifications selected from 2'-O-methyl, 2'-deoxy-2-'fluoro, 2'-deoxy, and deoxyabasic modifications and a method of use therein.

The Examiner acknowledges that the instant application is a national stage entry of PCT/US04/26930 filed August 20, 2004.

The instant application has been afforded priority to August 20, 2004, which is the filing date of PCT/US04/26930 because support for the invention as now claimed cannot be found in any other parent applications. Specifically, support for a chemically modified nucleic acid molecule complementary to a human NOGO receptor RNA comprising SEQ ID NO:325, wherein about 50 to 100 percent of the nucleotides in the sense strand and about 50 to 100 percent of the nucleotides in the antisense strand are chemically modified with modifications independently selected from 2'-O-methyl, 2'-deoxy-2-'fluoro, 2'-deoxy, phosphorothioate and deoxyabasic modifications cannot be found. Also, support for a chemically modified nucleic acid molecule comprising a sense strand and an antisense strand wherein the antisense strand is complementary to a human NOGO receptor RNA comprising SEQ ID NO:325, wherein each strand is 18 to 27 nucleotides in length, wherein at least 50% of the nucleotides in each of the sense and antisense strands of the chemically modified double stranded nucleic acid molecule are modified with modifications selected from 2'-O-methyl, 2'-deoxy-2-'fluoro, 2'-deoxy,

and deoxyabasic modifications cannot be found.

In summary, Applicant does not receive the benefit of any earlier filed application because the prior application(s) do not provide adequate support for the claims of the instant application and thus Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120. If Applicants believe that they are entitled to an earlier priority date, then Applicant must point, with particularity, to where support for the instant invention can be found in the specification of the prior application(s).

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claims 1, 3, 13-21, 30, 31, 36-41, and 46 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1, 3, 14-21, 30, and 35-39 of copending Application No. US Publication 20050182008. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

Claims 1, 3, 13-21, 30, 31, 36-41, and 46 of this application conflict with claim1, 3, 14-21, 30, and 35-39 of copending Application No. US Publication 20050182008. 37

CFR 1.78(b) provides that when two or more applications filed by the same applicant contain conflicting claims, elimination of such claims from all but one application may be required in the absence of good and sufficient reason for their retention during pendency in more than one application. Applicant is required to either cancel the conflicting claims from all but one application or maintain a clear line of demarcation between the applications. See MPEP § 822.

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The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 42-45 and 47 are provisionally rejected under the judicially created doctrine of double patenting over claims 1, 3, 14-21, 30, and 35-39 of copending Application No. US Publication 20050182008. This is a provisional double patenting

rejection since the conflicting claims have not yet been patented. Although the conflicting claims are not identical, they are not patentably distinct from each other because:

The chemically modified nucleic acid molecule complementary to a human NOGO receptor RNA comprising SEQ ID NO:325 and a method of use therein of claims 42-45 and 47 of the instant invention embraces the chemically modified nucleic acid molecule complementary to a human NOGO receptor RNA comprising SEQ ID NO:325 and the method of use therein of the copending application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 46 and 47 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of modulating the expression of human NOGO receptor gene in a cell *in vitro*, comprising administering for a chemically modified nucleic acid molecule complementary to a human NOGO receptor RNA comprising SEQ ID NO:325, wherein about 50 to 100 percent of the nucleotides in the sense strand and about 50 to 100 percent of the nucleotides in the antisense strand are chemically modified with modifications independently selected from 2'-O-methyl, 2'-

deoxy-2-'fluoro, 2'-deoxy, phosphorothioate and deoxyabasic modifications under condition suitable for modulating the expression of NOGO receptor gene in the cell, or a method of modulating the expression of human NOGO receptor gene in a cell *in vitro*, comprising administering for a chemically modified nucleic acid molecule complementary to a human NOGO receptor RNA comprising SEQ ID NO:325, wherein at least 50% of the nucleotides in each of the sense and antisense strands of the chemically modified double stranded nucleic acid molecule are modified with modifications selected from 2'-O-methyl, 2'-deoxy-2-'fluoro, 2'-deoxy, and deoxyabasic modifications under condition suitable for modulating the expression of NOGO receptor gene in the cell, does not reasonably provide enablement for a method of modulating the expression of human NOGO receptor gene in a cell *in vivo*, comprising administering for a chemically modified nucleic acid molecule complementary to a human NOGO receptor RNA comprising SEQ ID NO:325, wherein about 50 to 100 percent of the nucleotides in the sense strand and about 50 to 100 percent of the nucleotides in the antisense strand are chemically modified with modifications independently selected from 2'-O-methyl, 2'-deoxy-2-'fluoro, 2'-deoxy, phosphorothioate and deoxyabasic modifications under condition suitable for modulating the expression of NOGO receptor gene in the cell, or a method of modulating the expression of human NOGO receptor gene in a cell *in vivo*, comprising administering for a chemically modified nucleic acid molecule complementary to a human NOGO receptor RNA comprising SEQ ID NO:325, wherein at least 50% of the nucleotides in each of the sense and antisense strands of the chemically modified double stranded nucleic acid

molecule are modified with modifications selected from 2'-O-methyl, 2'-deoxy-2-'fluoro, 2'-deoxy, and deoxyabasic modifications under condition suitable for modulating the expression of NOGO receptor gene in the cell. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or the invention commensurate in scope with these claims. This is a scope enablement rejection.

There are many factors to be considered when determining whether there is sufficient evidence to support determination that a disclosure does not satisfy the enablement requirements and whether any necessary experimentation is undue. These factors have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and the breadth of the claims:

Claim 46 is drawn to a method of modulating the expression of human NOGO receptor gene in a cell *in vitro*, comprising administering for a chemically modified nucleic acid molecule complementary to a human NOGO receptor RNA comprising SEQ ID NO:325, wherein about 50 to 100 percent of the nucleotides in the sense strand and about 50 to 100 percent of the nucleotides in the antisense strand are chemically modified with modifications independently selected from 2'-O-methyl, 2'-deoxy-2-'fluoro,

2'-deoxy, phosphorothioate and deoxyabasic modifications under condition suitable for modulating the expression of NOGO receptor gene in the cell. Claim 47 is drawn to a method of modulating the expression of human NOGO receptor gene in a cell *in vitro*, comprising administering for a chemically modified nucleic acid molecule complementary to a human NOGO receptor RNA comprising SEQ ID NO:325, wherein at least 50% of the nucleotides in each of the sense and antisense strands of the chemically modified double stranded nucleic acid molecule are modified with modifications selected from 2'-O-methyl, 2'-deoxy-2-'fluoro, 2'-deoxy, and deoxyabasic modifications under condition suitable for modulating the expression of NOGO receptor gene in the cell. The broadness of the methods recited in the claims implies *in vivo* applicability for enablement purposes. The nature of the invention, therefore, requires the knowledge of using chemically modified nucleic acid molecules that can be delivered to cells or tissues in a subject (*in vivo*) such that the expression of human NOGO receptor gene is modulated.

<u>The amount of direction or guidance and presence/absence of working examples:</u>

The specification provides examples wherein siNA constructs are tested for efficacy in reducing NOGO and/or NOGO receptor RNA expression in A549 cells *in vitro* (cell culture) (see Example 9 and Figure 22). The specification teaches, "The invention features a method for modulating the expression of more than one NOGO and/or NOGO receptor gene within a cell comprising (a) synthesizing siNA molecules of the invention, which can be chemically-modified, wherein the siNA comprises a single stranded sequence having complementarity to RNA of the NOGO and/or NOGO

receptor gene; and (b) contacting the cell *in vitro* or *in vivo* with the siNA molecule under conditions suitable to modulate the expression of the NOGO and/or NOGO receptor genes in the cell' (see page 59, third paragraph). The specification does not demonstrate any correlation with the modulation of NOGO receptor RNA in cell culture and modulating the expression of NOGO receptor RNA in any cell or tissue *in vivo* (whole organism). The specification does not present any examples wherein a chemically modified nucleic acid molecule complementary to a human NOGO receptor RNA was delivered to cells *in vivo* (whole organism), nor wherein a chemically modified nucleic acid molecule complementary to a human NOGO receptor RNA modulated the expression of NOGO receptor RNA in cells or tissues *in vivo* (whole organism).

The state of the prior art and the predictability or unpredictability of the art:

The following references are cited herein to illustrate the state of the art of delivery of chemically modified nucleic acid molecules into targeted cells, tissues, and organs *in vivo*:

Lu et al. (2005) in *RNA Interference Technology* (Cambridge, Appasani, ed.), page 303, state that "Unlike *in vitro* transfection of siRNA into cells, *in vivo* delivery of siRNA into targeted tissue in animal models is much more complicated, involving physical, chemical and biological approaches, and in some cases their combination." Therapeutic applications, however, clearly depend upon optimized local and systemic delivery of siRNA *in vivo*. "....limited reports of *in vivo* studies have indicated a lack of effective delivery methods for siRNA agents." "...the two most critical hurdles are maintaining its [siRNA] stability *in vivo* and delivery to disease tissues and cells."

Samarsky et al. in *RNA Interference Technology,* (2005) pages 389-394, appear to agree with Lu et al., stating that "Delivery of RNAi to target cells and tissues in mammalian organism[s] is considerably more difficult than in cultured cells. This step is likely to be a critical bottleneck in the *in vivo* application of RNAi." "One major remaining obstacle is the efficient delivery of RNAi triggers to target tissues *in vivo*." (page 394).

Paroo et al. (Trends in Biotechnology, 2004 Vol. 22:390-394) address the unpredictability associated with siRNA therapy with the following statements: "In contrast to the great success of synthetic siRNA in mammalian cell culture, there have been few reports employing synthetic siRNA in animals. Developing siRNA for efficient gene silencing *in vivo* is likely to be more challenging and many issues must be addressed before use in animals can become routine". Paroo et al. also state, "Crucial pharmacological and chemical challenges will need to be addressed before siRNA can fulfill its immense promise" (see page 393, last paragraph).

The level of skill in the art:

The level of skill in the art is deemed to be high.

The quantity of experimentation necessary:

A review of the instant application fails to find adequate guidance or any disclosure exemplifying the *in vivo* applications as broadly claimed. Although Applicants clearly recognize the potential of chemically modified nucleic acid molecules for modulating NOGO receptor expression *in vivo,* Applicants do not teach the ordinary artisan how to effectively deliver chemically modified nucleic acid molecules to target tissues and cells *in vivo* to modulate expression of a target gene. A review of the

instant application finds working examples directed to an *in vitro* method of reducing NOGO receptor RNA expression in A549 cells, the method comprising modulating NOGO receptor gene expression by administration of siNA constructs directed to NOGO receptor RNA. No technical guidance or exemplary disclosure is provided regarding the use of the claimed methods for targeting NOGO receptor genes in living organisms, including any mammal, using chemically modified nucleic acid molecules. As the references above indicate, cell culture results are not readily extrapolated to *in vivo* applications.

Thus, it is maintained that the prior art at the time of Applicant's filing would not enable the use of chemically modified nucleic acid molecules *in vitro* to support claims directed to the *in vivo* use of chemically modified nucleic acid molecules, let alone claims directed to delivering chemically modified nucleic acid molecules *in vivo*. Accordingly, one skilled in the art, being unable to use the prior art for such guidance, must necessarily find such guidance from the specification. However, one of skill would not find the guidance provided in the specification in the form of *in vitro* examples enough to overcome the unpredictability and challenges of applying results from *in vitro* experiments to the *in vivo* methods of inhibition, as exemplified in the references above.

In order to practice the invention using the specification and the state of the prior art as outlined above, the quantity of experimentation required to practice the invention as claimed *in vivo* would require the *de novo* determination of those chemically modified nucleic acid molecules directed to the NOGO receptor gene that are successfully delivered to target sites in appropriate cells and/or tissues such that NOGO receptor

expression is modulated in a whole organism. Since the specification fails to provide any real guidance for methods of using chemically modified nucleic acid molecules *in vivo*, and since resolution of the various complications in regards to targeting a particular gene in a living organism is unpredictable, one of skill in the art would have been unable to practice the invention over the scope claimed without engaging in undue trial and error experimentation.

Thus, given the broad claims in an art whose nature is identified as unpredictable, the state of the prior art, the lack of guidance in the specification, the breadth of the claims and the quantity of experimentation necessary to practice the claimed invention, it would require undue experimentation to practice the invention commensurate in scope with the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3, 13-21, 30, 31, and 36-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over GenBank Accession Number NM_023004 (2003), in view of Groutsi et al. (Society of Neuroscience Abstracts, 2001 Vol. 27, No. 1, page 917), Hammond et al. (Nature Genetics 2001, Vol. 2:110-119), Elbashir et al. (EMBO Journal, 2001 Vol. 20:6877-6888), Matulic-Adamic et al. (US Patent No. 5,998,203), and Parrish et al. (Molecular Cell, 2000 Vol. 6:1077-1087).

Applicant is reminded that the instant application has been afforded priority to the filing date of PCT/US04/26930, which is August 20, 2004. For further explanation, see the discussion above under the heading "Priority".

Claims 1 and 46 are drawn to a chemically modified nucleic acid molecule comprising a sense strand and an antisense strand wherein the antisense strand is complementary to a human NOGO receptor RNA comprising SEQ ID NO:325, wherein each strand is 18 to 27 nucleotides in length, wherein about 50 to 100% of the nucleotides in each of the sense and antisense strands of the chemically modified double stranded nucleic acid molecule are modified with modifications selected from 2'-O-methyl, 2'-deoxy-2-'fluoro, 2'-deoxy, phosphorothioate and deoxyabasic modifications and a method of use therein. Clams 3, 13-21, 30, 31, and 36-41 are dependent on

claim 1 and include all the limitations of claim 1 with the further limitations wherein said chemically modified nucleic acid molecule comprise ribonucleotides; wherein one or more purine or pyrimidine nucleotides are present on the sense strand; wherein the purine nucleotide is a 2'-deoxy purine and the pyrimidine nucleotide is a 2'-deoxy-2'-fluoro pyrimidine nucleotide; wherein the sense strand comprises a terminal cap moiety at the 5' or 3' end, or both; wherein said terminal cap moiety is an inverted deoxy abasic moiety; wherein the antisense strand comprises 2'-deoxy-2'-fluoro pyrimidine nucleotides; wherein the purine nucleotide on the antisense strand is a 2'-methyl purine nucleotide or a 2'-deoxy purine nucleotide; wherein the antisense strand comprises a phosphorothioate internucleotide linkage at the 3' end of the antisense strand; wherein the 5'-end of the antisense strand includes a terminal phosphate group; and a chemically modified chemically modified nucleic acid molecule comprising a sense strand and an antisense strand, wherein the antisense strand is complementary to a NOGO receptor nucleotide sequence comprising SEQ ID NO:325, wherein about 50% to 100% of nucleotide positions in one or both strands of said chemically modified nucleic acid molecule are chemically modified in a pharmaceutically acceptable carrier or diluent. Claims 44, 45, and 47 are drawn to a chemically modified nucleic acid molecule comprising a sense strand and an antisense strand wherein the antisense strand is complementary to a human NOGO receptor RNA comprising SEQ ID NO:325, wherein each strand is 18 to 27 nucleotides in length, wherein at least 50% of the nucleotides in each of the sense and antisense strands of the chemically modified double stranded nucleic acid molecule are modified with modifications selected from 2'-

O-methyl, 2'-deoxy-2-'fluoro, 2'-deoxy, and deoxyabasic modifications, and a pharmaceutically acceptable carrier therein, and a method of use therein. Claims 42 and 43 are drawn to a chemically modified nucleic acid molecule comprising a sense strand and a separate antisense strand, wherein each strand is 18 to 27 nucleotides in length; an antisense strand and a sense strand are complementary to and comprise an 18 to 27 nucleotide sequence complementary to a human NOGO receptor RNA comprising SEQ ID NO:325; the sense strand includes a terminal cap moiety at the 5' or 3' end, or both; one or more of the nucleotide present in the sense strand or the antisense strand are 2'-O-methyl modified nucleotides; and one to ten or more of the pyrimidine nucleotides present on the sense strand or the antisense strand are 2'-deoxy-2-'fluoro pyrimidine nucleotides, and a pharmaceutically acceptable carrier therein.

GenBank Accession Number NM_023004 teaches the sequence of the human NOGO receptor gene.

Groutsi et al. teach antisense RNA to the NOGO receptor for promoting spinal cord regeneration (see Abstract).

Neither GenBank Accession Number NM_023004 nor Groutsi et al. teach a chemically modified nucleic acid molecule comprising a sense strand and an antisense strand wherein the antisense strand is complementary to a human NOGO receptor RNA comprising SEQ ID NO:325, wherein each strand is 18 to 27 nucleotides in length, wherein about 50 to 100% or at least 50% of the nucleotides in each of the sense and antisense strands of the chemically modified double stranded nucleic acid molecule are

modified with modifications selected from 2'-O-methyl, 2'-deoxy-2-'fluoro, 2'-deoxy, phosphorothioate and deoxyabasic modifications.

Hammond et al. teach that antisense and RNA interference are two methods of silencing expression of a gene and that RNA interference possesses characteristics that make it superior to antisense. For example, on page 110, first column, Hammond teaches that antisense methods are straightforward but suffer from "questionable specificity and incomplete efficacy". RNA interference on the other hand, "has been shown in diverse organisms to inhibit gene expression in a sequence-specific manner" (same page and column) and requires only a few molecules of dsRNA per cell to silence expression. Hammond also teaches that the RNA interference phenomenon in animals was discovered by researchers who were using antisense techniques and found that the use of double stranded instead of single-stranded RNAs reduced gene expression tenfold more efficiently (see paragraph bridging pages 110-111).

Elbashir et al. teach RNA interference (RNAi) is a newly discovered pathway of inhibiting gene expression by using an antisense-like mechanism. Specifically, Elbashir et al. teach short interfering RNAs (siRNAs) as mediators of RNAi and inhibitors of gene expression. Detailed protocols and methods are provided for designing, preparing, testing, and using siRNA to silence/inhibit expression of virtually any known gene. Elbashir et al. teach siRNAs, wherein each strand is 21-23 nucleotides in length and wherein at least 19 nucleotides of the sense strand are complementary to the antisense strand (see Abstract). Elbashir et al. teach modification of the internal nucleotides with 2'-deoxy or 2'-O-methyl modifications (see Abstract and Figure 4). Elbashir et al. teach

that duplexes, 21 nucleotides in length, with 2 nt 3' overhangs, were the most efficient triggers of sequence-specific mRNA degradation. Elbashir et al. teach 2'-deoxythymidine in the 3' overhang (see Figures 7 and 8). Elbashir et al. teach that a 5'-phosphate on the target-complementary strand of a siRNA duplex is required for siRNA function. Elbashir et al. also teach siRNA duplexes were incubated in a *D.melanogaster* RNAi/translation reaction for 15 min prior to addition of mRNAs, where the reaction mixture constitutes a pharmaceutically acceptable carrier or diluent. Elbashir et al. also teach complete substitution of one or both siRNA strands by 2'-deoxy residues and complete substitution by 2'-O-methyl residues (see page 6882, first column). It is noted that complete substitution of one or both siRNA strands by 2'-deoxy residues or by 2'-O-methyl residues abolished RNAi activity, however, the instant claims do not recite any functional language, therefore, the skilled artisan would have been motivated to incorporate extensive substitutions/chemical modifications to a siRNA to determine overall RNAi activity.

Matulic-Adamic et al. teach chemical modifications of double stranded nucleic acid structures (see Abstract). The double stranded nucleic acid RNA molecules of Matulic-Adamic et al. are taught to be targeted to virtually any RNA transcript and achieve efficient cleavage (see column 1) and to be sufficiently complementary to a target sequence to allow cleavage. Matulic-Adamic et al. teach the incorporation of chemical modifications at the 5' and/or 3' ends of the double stranded nucleic acids to protect the enzymatic nucleic acids from exonuclease degradation, which improves the overall effectiveness of the nucleic acid

molecules (see column 2). Matulic-Adamic et al. teach base, sugar and/or phosphate modification, as well as terminal cap moieties at the 5'-cap, 3'-cap, or both. Specifically, 3'-phosphorothioates, inverted abasic moieties, and 2'-O-methyl modifications are utilized. Matulic-Adamic et al. teach 2'deoxy nucleotides and 2'-deoxy-2'-halogen nucleotides, wherein Br, CL and F are representative halogens (see column 3, for example). The modifications can be in one or both of the strands and can be modifications of different types within the same structure.

Parrish et al. teach chemically synthesized double stranded siRNA molecules comprising various modifications in the sense or antisense strand, including 2'-deoxy-2'-fluoro modifications (see Figure 5). One or both strands comprise modifications. Parrish et al. teach that certain modifications were well tolerated on the sense, but not the antisense strand, indicating that the two trigger strands have distinct roles in the RNA interference process (see Summary).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to make a chemically modified nucleic acid molecule comprising a sense strand and an antisense strand wherein the antisense strand is complementary to a human NOGO receptor RNA comprising SEQ ID NO:325 using the sequence taught by GenBank Accession Number NM_023004, the motivation of Groutsi et al. and Hammond et al., and following the methods of Elbashir et al., Matulic-Adamic et al., and Parrish et al. It would have been obvious to have about 50 to 100% or at least 50% of the nucleotides in one or both strands be chemically modified using the teachings and motivation of Elbashir et al., Matulic-Adamic et al., and/or Parrish et al. It

would have been obvious to have the chemically modified nucleic acid molecule comprised in a pharmaceutically acceptable carrier or diluent using the teachings and motivation of Elbashir et al.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of filing to incorporate about 50% to 100% or at least 50% of the nucleotides in one or both stands of the chemically modified nucleic acid molecule be 2'-O-methyl nucleotides or 2'-deoxy-2'-fluoro pyrimidine nucleotides to determine the tolerance of chemical modifications for RNAi activity as taught by Elbashir et al. It would have been obvious to incorporate a terminal cap moiety on one of the ends of the sense strand since Matulic-Adamic et al. taught such modifications protect the nucleic acid from exonuclease degradation. It would have been obvious to incorporate a phosphorothioate internucleotide linkage at the 3' end of the antisense strand or a terminal phosphate group at 5'-end of the antisense strand since either Elbashir et al., Matulic-Adamic et al., and/or Parrish et al. teach such modifications protect the nucleic acid from nuclease attack.

It would have been *prima facie* obvious to one of ordinary skill in the art to substitute the antisense RNA complementary to NOGO receptor taught by 'Groutsi et al. with a chemically modified nucleic acid molecule comprising a sense strand and an antisense as instantly claimed since Hammond et al. taught that RNA interference is superior to antisense.

One of ordinary skill in the art would have been motivated to make a chemically modified nucleic acid molecule comprising a sense strand and an antisense strand

wherein the antisense strand is complementary to a human NOGO receptor RNA comprising SEQ ID NO:325 since Groutsi et al. taught the desirability of using nucleic acid inhibitors of gene expression to inhibit NOGO receptor gene expression for the purpose of promoting spinal cord regeneration. One would have been motivated to incorporate 2'-O-methyl or 2'-deoxy-2-fluoro nucleotide modifications into the chemically modified nucleic acid molecule since these modifications were known in the art to add benefits to double stranded nucleic acids such as protection from exonuclease degradation and improve uptake of the nucleic acid (see Elbashir et al., Matulic-Adamic et al., and Parrish et al.). It was well known in the art at the time of filing to incorporate one or more modifications, including 2'-O-methyl or 2'-deoxy-2-fluoro nucleotide modifications, into oligonucleotides, as evidenced by Elbashir et al., Matulic-Adamic et al., and Parrish et al. Elbashir et al. demonstrated both 2'-deoxy and 2'-O-methyl modifications of double stranded oligonucleotides at the time the invention was made. Matulic-Adamic et al. taught double stranded oligonucleotides comprising more than one specific type of modification. Additionally, Parrish et al. teach various modifications to double stranded duplexes and teach that different modifications are tolerated at different locations of the duplex. Elbashir et al. and Parrish et al. demonstrate the routine nature of testing various chemical modifications for optimization and stabilization of a double stranded duplex. The cited art demonstrates that the specific modifications were extensively described in the art. One of skill in the art would be motivated to test modifications that are known to benefit oligonucleotide delivery and apply each of them to a double stranded nucleic acid molecule, such as a siRNA in order to stabilize and

optimize delivery of the nucleic acid. One of skill in the art would be motivated to incorporate chemical modifications to about 50% to 100% or at least 50% of the nucleotide positions in one of the strands of the nucleic acid molecule to test the overall effect on RNAi activity as taught by Elbashir et al. One of skill in the art would be motivated to have the chemically modified nucleic acid molecule comprised in a pharmaceutically acceptable carrier or diluent to facilitate its delivery *in vitro* as taught by Elbashir et al.

One of ordinary skill in the art would have been motivated to substitute the antisense RNA complementary to NOGO receptor taught by Groutsi et al. with a chemically modified nucleic acid molecule comprising a sense strand and an antisense as instantly claimed since it is obvious to substitute one functional equivalent for another, particularly when they are to be used for the same purpose. See MPEP 2144.06. For further discussion, see the post-filing reference of Scanlon, KJ (Current Pharmaceutical Biotechnology, 2004 Vol. 5:415-420).

There would be a reasonable expectation of success to apply each of the claimed modifications to the chemically modified nucleic acid molecules of the claimed invention because the chemistry was well known to one of ordinary skill in the art at the time the invention was made (see Elbashir et al., Parrish et al., and Matulic-Adamic et al.) and merely selecting combinations of such modifications is considered a design choice. There would be a reasonable expectation of success to apply chemical modifications to about 50% to 100% or at least 50% of the nucleotide positions in one or both strand(s) of the siRNA molecule since Elbashir et al. taught the design of such

nucleic acids was known to be successful in the art at the time the invention was made. Therefore, one would reasonably expect for such modifications to benefit the chemically modified nucleic acid molecules as instantly claimed.

One of ordinary skill in the art would have expected success at substituting the antisense RNA complementary to NOGO receptor taught by Groutsi et al. with a chemically modified nucleic acid molecule comprising a sense strand and an antisense as instantly claimed because the substitution of one known element for another would have yielded predictable results at the time of the invention.

Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was filed.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is 571-272-0758. The examiner can normally be reached on 9 am - 5 pm M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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tcg
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/Terra Cotta Gibbs/